Evaluation of hybrid $^{68}$Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy

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Short running foot line: PSMA-ligand PET/CT for restaging of PCa
Abstract

**Introduction:**

Expression of prostate-specific membrane antigen (PSMA) is increased in prostate cancer. Recently, $^{68}\text{Ga-PSMA}$ (Glu-NH-CO-NH-Lys-(Ahx)-$^{68}\text{Ga(HBED-CC)}$) has been developed as a novel PSMA-ligand. The aim of this study was to investigate the detection rate of $^{68}\text{Ga-PSMA}$ PET/CT in patients with biochemical recurrence after radical prostatectomy.

**Methods:**

248 of 393 patients were evaluable for a retrospective analysis. Median PSA-level was 1.99ng/mL (range 0.2-59.4ng/mL). All patients underwent contrast-enhanced PET/CT after injection of $155\pm 27\text{MBq}^{68}\text{Ga-PSMA}$-ligand. The detection rates were correlated with PSA-level and PSA-kinetics. The influence of antihormonal treatment, primary Gleason score as well as the contribution of PET and morphological imaging to the final diagnosis were assessed.

**Results:**

222 (89.5%) patients showed pathological findings in $^{68}\text{Ga-PSMA}$-ligand PET/CT. The detection rates were 96.8%, 93.0%, 72.7% and 57.9% for PSA-levels of $\geq 2$, $1-<2$, $0.5-<1$ and $0.2-<0.5$ng/mL, respectively. Whereas detection rates increased with higher PSA-velocity (81.8%, 82.4%, 92.1% and 100% in $<1, 1-<2, 2-<5$ and $\geq 5$ng/mL/y, respectively), no significant association could be found for PSA doubling-time (82.7%, 96.2%, 90.7% in $>6, 4-6$, and $<4$ months, respectively). $^{68}\text{Ga-PSMA}$-ligand PET (as compared to CT) exclusively provided pathological findings in 81 (32.7%) patients. In 61 (24.6%) patients it exclusively identified additional involved regions. In higher Gleason score ($\leq 7$ vs $\geq 8$) detection efficacy was
significantly increased (p=0.0190). No significant difference in detection efficacy was present regarding anti-androgen therapy (p=0.0783).

**Conclusion:**
Hybrid $^{68}$Ga-PSMA-ligand PET/CT shows substantial higher detection rates than reported for other imaging modalities. Most importantly, it reveals a high number of positive findings in the clinically important range of low PSA-values (<0.5ng/mL), which in many cases can substantially influence the further clinical management.

**Key Words:**
PSMA-ligand
PET/CT
hybrid imaging
prostate cancer
biochemical recurrence
INTRODUCTION

In biochemical recurrence after radical prostatectomy (RP) an increase of the PSA-level precedes a clinically detectable recurrence by months to years (1). However, it cannot differentiate between local, regional or systemic disease with the necessary precision which is essential for further disease management (2). Furthermore, PSA kinetics such as PSA velocity (PSAvel) and PSA doubling time (PSAdt) play an important role with high PSA-kinetics facilitating disease detection (3).

Morphological imaging methods exhibit considerable limitations: Sensitivity ranges between 25% and 54% for the detection of local recurrence by transrectal ultrasound (TRUS) or CT and is moderately improved by using functional MRI techniques (2,4). The sensitivity for detection of lymph node metastases of CT or MRI is reported to be 30-80% (5). USPIOs (ultra-small particles of iron oxides) proved to be very effective, however have not been approved by regulatory authorities so far (6).

Various targets have been addressed by molecular imaging to improve the detection of recurrent PC. Using PET-imaging mainly 11C- and 11F-labelled choline derivates have been used in the past (7–9). However, especially in patients with PSA-values below 3 ng/mL detection rate is only 40-60% (3,4,7). Recently, a new molecular probe targeting e.g. the gastrin releasing peptide receptor (GPRr) or the prostate-specific membrane antigen (PSMA) have been developed (10–12). PSMA is a membrane bound enzyme with significantly elevated expression in PC cells in comparison to benign prostatic tissue (13). The localization of the catalytic site of PSMA in the extracellular domain allows the development of small specific inhibitors that are internalized after ligand binding (14). Older agents targeting the intracellular domain of PSMA showed disappointing results due to low image contrast, low sensitivity or high background signal (15). The recent development of $^{68}$Ga-PSMA (Glu-NH-CO-NH-Lys-(Ahx)- $^{68}$Ga(HBED-CC)) as an
extracellular PSMA-inhibitor for PET-imaging demonstrated high specificity for PSMA tumor expressing cells as well a high and specific uptake in a mouse model (16). A first preliminary study in PC patients revealed a higher image contrast and detection rate in comparison to $^{18}$F-Choline (17). In addition, further preliminary data in primary PC back the high specificity of $^{68}$Ga-PSMA-ligand PET-imaging ranging over 95% both at patient and field-based analysis for lymph node staging validated by extended pelvic lymph node dissection (18). Most recently, a large study including patients with different primary treatment was published encompassing patients with recurrent prostate cancer supporting high detection rates (19). Consequently, PSMA-targeting holds promise in being a superb biomarker for early detection of recurrent disease allowing adequate stratification of patients for optimal treatment planning. Thus, the purpose of our study was to assess the value of $^{68}$Ga-PSMA-ligand PET/CT for the detection and localization of recurrent disease in a large homogenous series of patients after radical prostatectomy. Specifically, we aimed to describe the detection rate as a function of the absolute PSA-level and PSA-kinetics as well as the evaluation of the diagnostic performance compared to primary histological differentiation and antihormonal treatment.

**MATERIALS AND METHODS**

**Patients**

393 consecutive patients who underwent $^{68}$Ga-PSMA-ligand PET/CT imaging for recurrent PC were extracted from the institutions’ database (11/2012 to 04/2014). Only patients who had undergone RP, whose PSA-level was $\geq 0.2$ng/mL and had not received chemotherapy were included (Fig.1). In total, 248 patients were included in this retrospective study. Patient
characteristics are summarized in Tab.1. 70 patients had received androgen-deprivation therapy within the last six month prior to the examination.

All patients gave written informed consent for the purpose of anonymized evaluation and publication of their data. All reported investigations were conducted in accordance with the Helsinki Declaration and with national regulations. The study was approved by the Ethics Committee of the Technical University Munich (permit 5665/13).

The serum PSA level at the time of the PET/CT scan was available in all patients. In addition, in 144 patients PSA kinetics (PSAvel and PSAdt) were calculated as described previously \(^{(20)}\). Only patients who were able to provide at least two PSA measurements after PSA progression (i.e., at least 3 PSA values) and in whom therapy had not been changed within the last 6 months prior to imaging were included in this subgroup analysis.

**Synthesis And Application Of \(^{68}\)Ga-PSMA-Ligand**

Images were obtained with the \(^{68}\)Ga-labelled HBED-CC \((16)\) that was synthesized as described previously \((21)\). The ligand was labelled with \(^{68}\)Ga\(^{3+}\) (half-life 67.6 min) from a \(^{68}\)Ge/\(^{68}\)Ga radionuclide generator (iThemba Labs, South Africa) by means of a fully automated module (Scintomics, Germany) and a GMP grade disposable cassettes and reagent kit (ABX, Germany) \((16,22)\). The final product was dissolved in isotonic phosphate-buffered saline (PBS) with subsequent sterile filtration.

The \(^{68}\)Ga-PSMA-ligand complex solution was applied to patients via an intravenous bolus (mean 155.5±27.4 MBq, range 88–240 MBq). Variation of injected radiotracer activity was caused by
the short half-life of $^{68}$Ga and variable elution efficiencies obtained during the lifetime of the $^{68}$Ge/$^{68}$Ga radionuclide generator.

**Imaging Protocol**

PET acquisition was started at a mean time of 54.2 min ± 7.1 after tracer injection (range 41-74 minutes). All patients underwent $^{68}$Ga-PSMA-ligand PET/CT on a Biograph mCT scanner (Siemens Medical Solutions, Erlangen, Germany). First a diagnostic CT scan was performed in the portal venous phase 80 s after intravenous injection of contrast agent (Imeron 300) followed by the PET scan. All patients received diluted oral contrast (300 mg Telebrix) and a rectal filling with a negative contrast agent (100–150 mL). All PET scans were acquired in 3D-mode with an acquisition time of 3-4 min per bed position. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively by an ordered-subsets expectation maximization algorithm (four iterations, eight subsets) followed by a postreconstruction smoothing Gaussian filter (5-mm full width at one-half maximum).

**Image Analysis**

All images were read by one board certified nuclear medicine physician and one board certified radiologist. Primarily $^{68}$Ga-PSMA-ligand PET images and CT were read separately followed by a final consensus read. All lesions suspicious for recurrent PC were noted and grouped into: (a) local recurrence, (b) lymph node metastases (discrimination into pelvic, retroperitoneal and supradiaphragmatic location), (c) bone metastases and (d) other metastases (e.g. lung, liver).
To demonstrate the individual contribution of PET and CT for the final diagnosis, for every lesion both the contribution of PET and/or CT for defining malignancy was noted. In PET any focal uptake of $^{68}$Ga-PSMA-ligand higher than the surrounding background and not associated with physiological uptake was considered suspicious for malignancy. For CT e.g. any pelvic/retroperitoneal lymph node station containing lymph nodes measuring at least 8 mm or any distinct sclerotic lesion not being associated with degenerative changes were judged as positive $^4$.

**Statistical Analysis**

The detection rate (number of patients with at least one positive finding) was plotted against the absolute PSA-value and PSA kinetics. Two-sample t tests were used to evaluate differences between single groups (Gleason Score, antihormonal treatment) as well as Mann–Whitney U tests to evaluate differences concerning PSA values between groups with and without pathological uptakes. All test were performed two-sided and a level of significance of $\alpha=5\%$ was used. Statistical analyses were conducted with software (MedCalc, version 13.2.0, 2014; MedCalc, Ostend, Belgium).
RESULTS

Detection Efficacy

*PSA-Level.* Of the 248 patients, 222 (89.5%) showed one or more localized areas suspicious for recurrent PC. The detection efficacy of $^{68}$Ga-PSMA-ligand PET/CT was 96.8% (120/124) for a PSA value $\geq 2$ ng/mL, 93.0% (67/72) for a PSA value 1-<2 ng/mL, 72.7% (24/33) for a PSA value 0.5-<1 ng/mL and 57.9% (11/19) for a PSA value 0.2-<0.5 ng/mL (Fig.2A). The different regions involved by recurrent disease are listed in Tab.2. Mean PSA was significantly lower in patients with negative $^{68}$Ga PSMA-ligand PET/CT compared to positive patients (p=0.0080; Tab.3).

PSA-Kinetics. PSAvel ranged from 0.1 to 42.5 ng/mL per year. The detection rates of $^{68}$Ga-PSMA-ligand PET/CT were 81.8% (54/66), 82.4% (14/17), 92.1% (35/38) and 100% (23/23) in patients with PSAvel values of, respectively, less than 1 ng/mL/y, 1–2 ng/mL/y, 2–5 ng/mL/y, and greater than 5 ng/mL/y (Figure 2B). Despite a strong tendency to higher PSAvel in patients with a positive $^{68}$Ga PSMA-ligand PET/CT compared to negative patients no statistical significance was reached (p=0.0532; Tab.3).

PSAdt values ranged between 0.37 and 158 months. The detection rates of $^{68}$Ga-PSMA-ligand PET/CT were 82.7% (62/75), 96.2% (25/26), 90.7% (39/43) in patients with PSAdt values of greater than 6 months, 4–6 months, and up to 4 months, respectively (figure 1C). Mean PSAdt was not significantly different in patients with $^{68}$Ga PSMA-ligand PET/CT negative findings compared to positive patients (p=0.2971; Tab.3).

Contribution Of PET And Morphological Imaging For Lesion Detection
The number and percentage of patients in which PET and CT were concordantly detecting lesions or in which PET or CT exclusively defined recurrent disease or showed additional involved regions (outside of primarily detected regions) is given in Fig.3. Notably, whereas $^{68}$Ga-PSMA-ligand PET (as compared to CT) exclusively provided relevant diagnostic information in 81 (32.7%) of the patients, CT (as compared to PET) was only able to exclusively provide the diagnostic information in 3 (1.2%) of the cases. Moreover, in 61 (24.6%) of the patients PET was able to identify additional involved regions compared to 17 (6.9%) patients in which CT showed additional regions (table 4). In most of the cases in which PET provided additional information lymph node metastases, local recurrence or bone metastases could not be identified by CT (representative examples are given in figures 4-6). Most of the lesions in which CT provided exclusive information were (sclerotic) bone or lung metastases.

**Influence Of Anti-Androgen Therapy And Primary Histological Differentiation**

In our patient collective no significant difference in detection efficacy could be observed with regard to anti-androgen therapy ($p=0.0783$). Lesions were detected in 95.7% (67/70) of patients with anti-androgen therapy and 87.1% (155/178) of patients without anti-androgen therapy. Notably, PSA-values were significantly higher in patients with vs. without antihormonal treatment ($8.11 \pm 10.83$ vs. $2.93 \pm 3.11$ ng/mL)

With respect to histological differentiation of the primary PC, $^{68}$Ga-PSMA-ligand PET/CT was positive in 86.7% (111/128) of patients with a Gleason score $\leq 7$ and in 96.8% (90/93) of patients with a Gleason score $\geq 8$ ($p=0.0190$). No difference in PSA-values was present between these two groups (PSA mean/median: $4.23/1.90$ vs. $4.89/2.2$ ng/mL).
DISCUSSION

PSA relapse after radical prostatectomy is a common clinical scenario. In this context, biochemical failure defined by a confirmed PSA value of >0.2 ng/mL after RP occurs long before recurrent disease can be localized clinically or by imaging. The goal in these patients is to distinguish whether disease relapse is localized to the prostate bed or whether metastatic disease is present as this impacts further treatment. To date, the detection of lesions in biochemical recurrence (esp. at PSA-values below 1 ng/mL) of PC is a major challenge for all imaging modalities including PET with a variety of tracers (4,5,9).

In this study we describe the detection rate of hybrid PET/CT imaging using a novel $^{68}$Ga-PSMA-ligand as a PET-tracer in a large number of patients with biochemical recurrence after RP. Despite being retrospective nature the strength of our study consists in a homogenous patient selection. Our results show a considerable higher detection of hybrid PET/CT imaging using the $^{68}$Ga-PSMA-ligand than reported for other PET tracers. Even in 67% of the patients with PSA-levels <1.0ng/mL the potential site of recurrence has been detected. Our data are in line with a data by Afshar-Oromieh et al. published online only most recently (19). However, in our study only patients with biochemical recurrence after radical prostatectomy were included consisting of a homogenous patient collective. In addition to the previous mentioned most recent work, we could show that compared to morphological imaging the information provided by $^{68}$Ga-PSMA-ligand PET was essential in 58% of the patients: In 33% the site of recurrence could only be detected by PET whereas in an additional 25% of the patients PET showed additional lesions not detectable by CT imaging.
Our results suggest that $^{68}$Ga-PSMA-ligand PET/CT is highly effective in PC restaging since in our study 89.5% of patients showed at least one lesion regarded as characteristic for PC. Our data based on a large and highly selected patient cohort are in line with preliminary reports by Afsar-Oromieh (17,23). Compared to reports in the literature stating detection rates between 34% and 88% for $^{11}$C-Choline, 43% to 79% for $^{18}$F-Choline and 59% to 80% for $^{11}$C-Acetate (7,24–30) [for a review see (31)] $^{68}$Ga-PSMA-ligand PET/CT offers a substantial higher detection efficacy. As known from other PET-tracers the detection rate of $^{68}$Ga-PSMA-ligand PET/CT also increases in parallel with raise of PSA-value (4). As an important finding, our study shows positive $^{68}$Ga-PSMA-ligand PET/CT findings for PSA-values <1 ng/mL in 67% of the patients. This is substantially higher than reported for choline-based PET-tracers showing detection rates between 19% and 36% at PSA-levels below 1-1.5 ng/mL (3,7,32,33). Thus, $^{68}$Ga-PSMA-ligand PET/CT improves lesion detectability in the group of patients at a very early state which potentially allows more tailored salvage therapies. Clinically the detection rate of 58% in patients with a PSA-level <0.5 ng/mL has particularly a clinical impact as urological guidelines [e.g. European Association of Urology (34)] define a PSA-value of 0.5 ng/mL as the upper limit for salvage radiation therapy. However, it has to be admitted that the overall detection rate of 89.5% implies a false-negative rate of 10.5% for $^{68}$Ga-PSMA-ligand PET/CT imaging as in the case of biochemical recurrence by definition viable recurring tumor must be present. In addition, it has to be mentioned that in this study the use of $^{68}$Ga-PSMA-ligand PET/CT was not limited to patients with prior negative conventional scans (e.g. bone scan, CT, MRI). Thus, using it in that preselected setting, the detection rate would potentially be different.

Similarly to choline-derivates our results state a higher detection rate in patients with higher PSAvel albeit the p-value of 0.0532 could be designed as borderline from a purist statistical point-of-view (3,32,35). Nevertheless, $^{68}$Ga-PSMA-ligand PET/CT offer a high rate of positive
findings also in patients with low changes in PSA kinetics with a detection rate of 81.8% compared to 12% for $^{11}$C-Choline at a PSAvel of 1ng/mL/Y (35). Notably, our data show no clear trend towards higher detection rates with decreasing PSAdt compared to reports for $^{11}$C- and $^{18}$F-Choline (32,35). However, especially at low PSA-value PSAdt is more susceptible to slight changes and thus not optimal suited in this patient collective. In addition, it has to be taken into account that data for PSAvel and PSAdt were only present in about 60% of the patients (as stated in sections Patients). Consequently, our data indicate that for $^{68}$Ga-PSMA-ligand PET/CT PSA-kinetics are not as crucial as for Cholin-derivates as the detection rate is over 75% also in patients with low PSAvel or high PSAdt.

The substantial contribution of $^{68}$Ga-PSMA-ligand PET in the setting of hybrid PET/CT is reflected by the fact that in 33% of cases the sites of recurrent disease were only identified by PET (figure 3/table 1S). In an additional 25% of cases PET was able to identify additional clinical relevant lesions not being detected by CT. However, the high number of patients in whom the diagnosis of recurrent disease was solely based on PET is not surprising as the limited role of CT imaging especially for local recurrence and lymph node metastases is well documented (2,36). Besides potential results derived from a bone scan in this patient cohort which with respect to the PSA-value would rather be low, this documents the high value of $^{68}$Ga-PSMA-ligand PET in a setting in which prior conventional imaging would have been negative. Indeed in our patient collective negative prior conventional imaging was not an inclusion criterion, however this comparison indicates the potential high number of findings in a negatively preselected group.

Our data show a statistical significant higher detection rate in patient with Gleason score $\geq 8$ vs $\leq 7$ which could be potentially attributed to the fact that immunohistochemically PSMA
expression is usually higher in lesions with higher Gleason score than in lesions with lower Gleason score (37). Our data show a trend towards a higher detection rate in patients with anti-androgen therapy within 6 months prior to $^{68}$Ga-PSMA-ligand PET/CT imaging. However, these data do not reach statistical significance and it has to be noted that mean PSA-values were significantly higher in patients with antihormonal treatment which could constitute a confounding factor. Nevertheless, there are reports stating higher PSMA-expression of prostate cancer tumor cells in the setting of antihormonal treatment (38,39) which could potentially be reflected in higher detection rates. This hypothesis has to be proven in further studies.

A major limitation of our study is the fact that histopathology as gold standard was only available in a minority of cases. In 12 patients $^{68}$Ga-PSMA-ligand PET/CT positive lymph node metastases were histological confirmed. However, a histopathological confirmation in all patients is not feasible due of practical and ethical issues in the setting recurrent prostate cancer. Nevertheless, in 35 patients $^{68}$Ga-PSMA-ligand PET/CT guided selective radiation therapy followed by a substantial decrease of PSA proved the nature of PSMA-positive lesions. In another 45 patients follow-up / other imaging modalities unanimously proved that the positive lesions were metastases of PC. So in total, in 37.1% (92/248) patients a comprehensive standard of reference (histopathology, decrease of PSA-level after targeted radiation therapy or undisputable follow-up/other imaging methods) was available. In all of these cases concordant results in correlation with the findings derived from $^{68}$Ga-PSMA-ligand PET/CT were present.

CONCLUSION
In this study $^{68}$Ga-PSMA-ligand PET/CT proved in a large number of patients with biochemical recurrence after RP a substantial higher detection efficacy than reported for other tracers. With a detection rate of $>90\%$ at PSA-levels over 1 ng/mL this method currently surpasses all other imaging modalities for restaging of PC. In patients in whom salvage therapies decision are pending $^{68}$Ga-PSMA-ligand PET/CT imaging can also be performed at lower PSA-level expecting a detection rate of approximately 50\% and offering the potential of guiding those treatments. In more than 50\% of the cases the information yielded by $^{68}$Ga-PSMA PET was crucial for the final diagnosis showing findings which have not been visualized by CT. In addition, the high tumor uptake of PSMA-inhibitors make these compounds in a subset of metastasized patients particularly attractive for endoradiotherapy. Hereby, imaging and therapeutic small molecule inhibitors of PSMA could potentially be used as theranostic strategy for patients with metastasized prostate cancer.

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REFERENCES:


Figure 1. Flow chart of patient selection
Figure 2. Detection rate of $^{68}$Ga-PSMA-ligand PET/CT in relation the PSA-level (2A), PSAvel (2B) and PSAdt (2C).
Figure 3. Contribution of PET and morphological imaging for lesion detection
Figure 4. Set of images of a 75 year old patient with status post radical prostatectomy (2000, Gleason Score 5, pT3b, pN1), radiation therapy (09/2011) and rising PSA-value of 1.09 ng/mL (10/2013). CT images (A) reveal no suspicious finding with a 5 mm lymph node behind the right external iliac vein. Corresponding PET (C) and fused PET/CT images (D) show an intense uptake
with a high lesion-to-background ratio in this small lymph node indicating a lymph node metastasis. The whole-body MIP (maximum-intensity-projection, B) displays this lymph node and demonstrates no other suspicious lesion. Selective lymph node picking was performed in 12/2013 which confirmed a single lymph node metastasis. Subsequently, the PSA-value dropped below detection limit (<0.07 ng/mL) without antihormonal treatment (last measurement 04/2014).
Figure 5. Set of images of a 73 year old patient with status post radical prostatectomy (9/2013, Gleason Score 9, pT3b, pN0, PSA nadir below detection limit). Increase of PSA-value to 2.0 ng/mL (12/2013) and start of antihormonal treatment. Fused PET/CT image (A) demonstrate high intense uptake in the lumbar spine with no suspicious osteoblastic lesion in the corresponding CT image (B). Four months after radiation a diffuse sclerosis can be found in a CT image (C) indicating posttherapeutic changes/progression.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>248</td>
</tr>
<tr>
<td>primary RP</td>
<td>241 (97.2%)</td>
</tr>
<tr>
<td>salvage prostatectomy after primary radiation therapy</td>
<td>7 (2.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>70 (46-85)</td>
</tr>
<tr>
<td>Primary Gleason score *</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>7 (6-10)</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.99 (0.2–59.4)</td>
</tr>
<tr>
<td>further treatment</td>
<td></td>
</tr>
<tr>
<td>No. of pts with external radiation after RP</td>
<td>20</td>
</tr>
<tr>
<td>No. of pts with antihormonal treatment during/within 6 month prior imaging</td>
<td>70</td>
</tr>
</tbody>
</table>

* In 27 of 248 patients no information concerning the initial Gleason score could be obtained since the primary treatment of several patients dated back between 10 and 20 years.
Table 2. Different regions involved by recurrent PC in $^{68}$Ga-PSMA-ligand PET/CT

<table>
<thead>
<tr>
<th>Region</th>
<th>No. (percentage) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>87 (35.1%)</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td></td>
</tr>
<tr>
<td>- abdomino-pelvic</td>
<td>130 (52.4%)</td>
</tr>
<tr>
<td>- supradiaphragmatic</td>
<td>13 (5.2%)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>89 (35.9%)</td>
</tr>
<tr>
<td>Other (lung, liver, …) metastases</td>
<td>13 (5.2%)</td>
</tr>
</tbody>
</table>
Table. 3 PSA-level and PSA-kinetics in patients with positive and negative findings in $^{68}$Ga-PSMA-ligand PET/CT.

<table>
<thead>
<tr>
<th></th>
<th>positive findings</th>
<th>no findings</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA-level (ng/mL)</td>
<td>4.78 (±7.00)</td>
<td>1.10 (±1.00)</td>
<td>0.0080</td>
</tr>
<tr>
<td>(N=222)</td>
<td>(N=26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSAvel (ng/mL/y)</td>
<td>3.88 (±6.52)</td>
<td>0.87 (±0.96)</td>
<td>0.0532</td>
</tr>
<tr>
<td>(N=126)</td>
<td>(N=18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSAdt (months)</td>
<td>10.02 (±15.65)</td>
<td>14.01 (±10.55)</td>
<td>0.2971</td>
</tr>
<tr>
<td>(N=126)</td>
<td>(N=18)</td>
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Data are given as mean values and standard deviation.
Table 4. Malignant lesions exclusively identified in $^{68}$Ga PSMA PET or CT

<table>
<thead>
<tr>
<th>Region/Combination of regions</th>
<th>$^{68}$Ga PSMA PET</th>
<th>CT</th>
<th>$^{68}$Ga PSMA PET</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR only</td>
<td>18</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN metastases only</td>
<td>31</td>
<td>1</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Bone metastases only</td>
<td>9</td>
<td>1</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>LR + LN metastases</td>
<td>7</td>
<td>2</td>
<td></td>
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<tr>
<td>LR + bone metastases</td>
<td>6</td>
<td>1</td>
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<tr>
<td>LN + bone metastases</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR + LN + bone metastases</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (lung, liver metastases, …)</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>total</td>
<td>81 (32.7%)</td>
<td>3  (1.2%)</td>
<td>61 (24.6%)</td>
<td>17 (6.9%)</td>
</tr>
</tbody>
</table>